HHS Public Access

Author manuscript

Bone. Author manuscript; available in PMC 2022 January 10.

Published in final edited form as:

Bone. 2021 December ; 153: 116184. doi:10.1016/j.bone.2021.116184.

Preclinical Models of Medication-related Osteonecrosis of the Jaw (MRONJ)

JI Aguirre[1,*], **EJ Castillo**[1], **DB Kimmel**[1]

[1]Department of Physiological Sciences, University of Florida (UF), Gainesville, FL.

Abstract

Medication-related osteonecrosis of the jaw (MRONJ) is a potentially severe adverse event affecting patients with cancer and patients with osteoporosis who have been treated with powerful antiresorptives (pARs) or angiogenesis inhibitors (AgIs). pARs, including nitrogen-containing bisphosphonates (N-BPs; e.g., zoledronic acid, alendronate) and anti-RANKL antibodies (e.g., denosumab), are used to manage bone metastases in patients with cancer or to prevent fragility fractures in patients with osteoporosis.

Though significant advances have been made in understanding MRONJ, its pathophysiology is still not fully elucidated. Multiple species have been used in preclinical MRONJ research, including the rat, mouse, rice rat, rabbit, dog, sheep, and pig. Animal research has contributed immensely to advancing the MRONJ field, particularly, but not limited to, in developing models and investigating risk factors that were first observed in humans. MRONJ models have been developed using clinically relevant doses of systemic risk factors, like N-BPs, anti-RANKL antibodies, or AgIs. Specific local oral risk factors first noted in humans, including tooth extraction and inflammatory dental disease (e.g., periodontitis, periapical infection, etc.), were then added. Research in rodents, particularly the rat, and, to some extent, the mouse, across multiple laboratories, has contributed to establishing multiple relevant and complementary preclinical models. Models in larger species produced accurate clinical and histopathologic outcomes suggesting a potential role for confirming specific crucial findings from rodent research. We view the current state of animal models for MRONJ as good. The rodent models are now reliable enough to produce large numbers of MRONJ cases that could be applied in experiments testing treatment modalities. The course of MRONJ, including stage 0 MRONJ, is characterized well enough that basic studies of the molecular or enzyme-level findings in different MRONJ stages are possible.

This review provides a current overview of the existing models of MRONJ, their more significant features and findings, and important instances of their application in preclinical research.

Keywords

MRONJ; ONJ; BRONJ; animal models; preclinical studies; bisphosphonates; RANKL-inhibitors

[*]Please address correspondence to: J. Ignacio Aguirre, D.V.M., Ph.D., DACLAM, Department of Physiological Sciences, Box 100144, JHMHC, University of Florida, Gainesville, FL 32610, Telephone: (352) 294-4038, FAX: (352) 392-5145, aguirrej@ufl.edu.

Conflict of Interest

The authors have no conflicts of interest.

A. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a potentially severe, adverse event defined as exposed bone or bone that can be probed through any fistula in the maxillofacial region that persists for more than eight weeks in patients with no history of radiation therapy or metastatic disease in the jaws, who have been treated with powerful antiresorptives (pARs) or angiogenesis inhibitors (AgIs)[1–7]. pARs, including nitrogen-containing bisphosphonates (N-BPs; e.g., zoledronate [ZOL], alendronate [ALN], pamidronate [PAM], etc.,) and anti-RANKL antibodies (e.g., denosumab), are used to manage hypercalcemia and bone metastases in patients with cancer[8–11] or to prevent fragility fractures in patients with osteoporosis[12]. Though pAR-related MRONJ is more common in patients with cancer (1.8–5% incidence) than with osteoporosis (0.01–0.03% incidence)[5, 6, 13, 14], all data suggest similar general MRONJ pathophysiology in cancer and osteoporosis patients[5, 6, 15].

Both clinical and preclinical data suggest that most MRONJ cases require systemic risk factors (e.g., pARs or AgIs) to be combined with local oral risk factors that include tooth extraction[5, 6, 15–20], inflammatory dental disease (e.g., periodontitis, periapical infection), trauma from removable oral prostheses, and potentially from placement of dental implants[5, 6, 15–18, 21–31]

In 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) updated its 2007 guidelines[32], with significant changes in the staging and definition for MRONJ, proposing that patients be classified into five stages: “at-risk” and stages 0–3[5]. Patients *at risk* are asymptomatic pAR-treated patients with no exposed bone. Patients in *stage 0* have no clinical evidence of necrotic bone but present with nonspecific symptoms or clinical and/or radiographic findings in the jaw. Though stage 0 in some ways appears to capture the clinical signs and symptoms of early-onset ONJ[5, 33–37], only 50% of *stage 0* patients ever progress to stages 1–3[38, 39]. Conversely, all patients with *stages 1–3* have necrotic bone exposed to the oral cavity or a fistula that probes to bone. Patients in *stage 1* are asymptomatic and have no evidence of infection. Patients in *stage 2* ONJ are symptomatic (pain, swelling, and erythema in the region surrounding the exposed necrotic bone) and have evidence of infection. Patients in *stage 3* are also symptomatic with infection. They also have at least one of the following: exposed necrotic bone extending beyond the alveolar ridge, pathologic fracture, fistula, oral antral or oral-nasal communication, osteolysis extending to the sinus floor, or inferior border of the mandible.

Though significant advances have been made in understanding and treating MRONJ, its pathophysiology is still not fully elucidated. Laboratory animal experimentation has been crucial to the investigation of many human diseases. In addition, animal research has contributed immensely to advance the MRONJ field, particularly, but not limited to, developing models for future use, investigating risk factors, and testing preventive or curative modalities. In this review, we provide an overview of the existing preclinical models of MRONJ, their significant features and findings, and important instances of their use in preclinical research.

B. Animal Experimentation for MRONJ

In general, animal models are used not only to study the development and progression of diseases but also to test new treatments before they are given to humans. It is rare to find a single preclinical model that mimics all elements of a disease process. The wide range of animal models now available for MRONJ is a testament to the hard work of numerous investigators from multiple laboratories, providing a broad spectrum of opportunities to apply them in a complementary manner. Animal experimentation has also allowed investigators to perform controlled procedures that model real clinical risk factors of the disease. For example, published MRONJ studies reflect treatment with systemic risk factors, like N-BPs[19, 21–24, 26, 40–42], anti-RANKL antibodies[43, 44], and AgIs[45, 46]. MRONJ models have also combined the administration of systemic factors (pARs and AgIs) with specific oral risk factors first noted in humans, including tooth extraction, inflammatory dental disease (e.g., periodontitis, periapical infection, etc.), and also implant placement. Others modeled MRONJ scenarios combining multiple oral risk factors (e.g., periodontitis or periapical infection followed by tooth extraction) or multiple systemic risk factors (e.g., adjuvant glucocorticoid treatment in addition to pARs).

C. Clinically appropriate dosing of N-BPs in animals

Sufficient information exists in the published literature to calculate clinically relevant absorbed doses of N-BPs in animal studies. The ready availability of such data makes allometric scaling unnecessary and inherently risky. Pharmacology studies strongly suggest that the most reliable method for determining clinically relevant absorbed doses of N-BPs in any animal is first to understand the minimum absorbed dose that completely prevents bone loss in newly-ovariectomized (OVX) animals of that species. The minimum absorbed dose is also the absorbed dose of any N-BP used in adult humans to stop bone loss and treat osteoporosis. To find this dose, all major N-BPs have been tested in the OVX rat[47–52]. For example, the minimum absorbed dose of ZOL that completely prevents bone loss in adult OVX rats is 8μg/kg IV 1X/mo[47]. The minimum dose of ALN that completely prevents bone loss in adult OVX rats is 15μg/kg subcutaneously (SC) 2X/wk[48]. The minimum dose of ibandronate that completely prevents bone loss in adult OVX rats is 4μg/kg SC 2X/wk[48, 51, 52]. The minimum dose of minodronate that completely prevents bone loss in adult OVX rats is 6μg/kg SC 2X/wk[49, 50]. These are the rat “osteoporosis” doses.

The minimum dose of risedronate that completely prevents bone loss in adult OVX mice is 20μg/kg SC 2X/wk[53], or 160μg/kg/mo SC. This is the mouse “osteoporosis” dose of risedronate. The minimum dose of ALN that completely prevents bone loss in adult OVX mice is 40μg/kg every 4 days[53] or 75μg/kg SC 2X/wk[54], or 280–600 μg/kg/mo SC of ALN. This is the mouse “osteoporosis” dose of ALN. No studies to establish the minimum dose of ZOL to prevent bone loss in adult OVX mice have been published. In this case, one can use the relative N-BP potencies to predict the minimum dose that prevents bone loss in adult OVX mice for ZOL and other N-BPs (Table 1A). Considering that ZOL is 15 times more potent than ALN in stopping OVX-induced bone loss in the adult rat, we can predict that the minimum dose of ZOL that completely prevents bone loss in adults OVX mice would be ~20–40 μg/kg/mo IV. This is the predicted “osteoporosis dose of ZOL in mice.

The next step is to find the relevant rat or mouse “oncology dose”. To do this, one considers the oncology:osteoporosis dose ratios of a single pAR in humans. There are two examples, ZOL, and denosumab, because these two pARs are routinely used for oncology and osteoporosis patients. The ZOL dose used in oncology patients is 4mg IV 1X/mo (48mg IV/yr)[55]. The ZOL dose used in osteoporosis patients is 5mg IV 1X/yr[56]. For ZOL, the ratio of the yearly oncology dose to the yearly osteoporosis dose in humans is 9.6:1. The denosumab dose used in cancer patients is 120mg SC 1X/mo (1440mg SC/yr)[55]. The denosumab dose used in osteoporosis patients is 60mg SC 2X/yr (120mg SC/yr)[56]. For denosumab, the ratio of the yearly oncology dose to the yearly osteoporosis dose in humans is 12:1. For ZOL and denosumab, the oncology dose can be approximated as about ten-fold greater than the osteoporosis dose. To predict a reasonable rat “oncology dose” for ZOL, one then multiplies 8μg/kg IV 1X/mo, the rat “osteoporosis dose,” by ten, giving 80μg/kg ZOL IV 1X/mo as the rat “oncology dose” (Table 1B). To predict a reasonable mouse “oncology dose” for ZOL, one multiplies 20–40μg/kg IV 1X/mo, the mouse “osteoporosis dose,” by ten, giving 200–400μg/kg ZOL IV 1X/mo as the mouse “oncology dose” (Table 1B).

For species in which OVX-induced bone loss does not reliably occur, such as the dog[57, 58], the minimum dose of N-BP that completely prevents OVX-induced bone loss cannot be assessed. When the benchmark of OVX-induced bone loss cannot be established in an animal, choosing a clinically relevant dose is much more difficult.

Perspective on the use of supra-clinical doses in animals

Conventional toxicity testing in animals is designed to use proposed clinically efficacious doses of an agent to disclose previously unidentified adverse effects of an agent before they are ever seen in humans. Applying supra-clinical doses of an agent in this setting is generally used for: a) producing enough toxic events to allow their identification and characterization, and b) learning for which toxic events to search in animals receiving proposed clinical doses. However, when, as with MRONJ, a toxic event is first identified in humans, toxicity testing in animals should be streamlined. Not only does the toxic event not need to be *newly* identified and characterized, but its potential risk factors are also already identified. The only need is to be sure that the toxic event in animals bears a solid resemblance to what has been recorded in humans. Thus, the goal becomes creating toxic events in animals by simulating the circumstances that produce the actual toxic event in humans.

Combining supra-clinical doses with risk factors during the initial design of potential animal models is a typical first step in verifying that an animal can express the toxic event. However, since humans express the toxic event at clinical doses, testing for the toxic event in animals bearing the risk factors and utilizing clinically relevant doses is eventually essential to judging the significance of an animal model[59]. Thus, for example, when a toxic event is produced in an animal only by excessive cumulative absorbed doses, further refinement of the model should be considered because it most likely lacks one or more of the underlying conditions that cause the disease in humans. In addition, one must consider the possibility that animal models that produce the toxic event only at supra-clinical doses may cause it only through pathways/mechanisms that differ from those which cause it in humans.

D. Animal Models of MRONJ:

To update the information about the preclinical investigation of MRONJ, we performed a survey of prior research literature between March 2003 and June 2021. We utilized academic research databases including Pubmed, Europe PMC, Embase, Medline through Pubmed, ScienceDirect, and Web of Science. The following combination of search terms was used: "*Osteonecrosis of the jaw*" **OR** "*ONJ*" **OR** "*BRONJ*" **OR** "*MRONJ*," **AND** "animals," **OR** "animal models," **OR** "*mouse*" **OR** "*mice*" **OR** "*rat*," **OR** "*rice rat*," **OR** "*Oryzomys*," **OR** "*rabbit*," **OR** "*dog*," **OR** "*pig*," **OR** "*sheep*." We selected only full-text articles published in English. Reviews about animal models of MRONJ or studies presenting exclusively *in vitro* data were excluded. In addition, animal studies involving pARs or AgIs that investigate only the postcranial skeleton were excluded. References were managed using the software (EndNote™, Thomson Reuters) and Excel. Two independent authors (JIA, EC) reviewed all titles and abstracts. Any disagreement between the evaluators was resolved by discussion and mutual agreement. If JIA and EC did not reach a consensus, the third author (DBK) took a final decision.

Multiple species have been used in preclinical studies associated with MRONJ, including the rat (*Rattus norvegicus*), mouse (*Mus musculus*), rice rat (*Oryzomys palustris*), rabbit (*Oryctolagus cuniculus*), dog (*Canis lupus familiaris*), sheep (*Ovis aries*), and pig (*Sus scrofa domesticus*) (Figure 1A). A total of 240 articles fulfilled the specified search criteria. Of these, ~60% (n= 145) utilized rats, ~27% (n= 65) mice, ~4% (n= 9) dogs, ~3% (n= 7) pigs, 2.5% (n= 6) rice rats, ~2% (n= 4) rabbits, and ~2% (n= 4) sheep (Figure 1A). The distribution of the number of MRONJ animal studies by species and year of publication is depicted in Figure 1B.

Small vertebrate species, such as mice and rats, have general conceptual advantages over larger vertebrate species. They do not require complex laboratory infrastructure, and they occupy less housing space per animal. Using small vertebrate species is advantageous because a broad range of specific reagents is available, including antibodies, biologics, cellular and molecular arrays, etc. Their low body weight makes treatments with rare test agents feasible because they require relatively small amounts of the drug. Furthermore, genetically engineered mice are widely available and relatively quickly made. Genetically engineered rats are rarely used, though CRISPR has made the genome editing process much more efficient and has improved prospects for transgenic rats[60]. Small vertebrate species also have disadvantages. While tooth extraction and implant placement are possible, the small size of the oral cavity and teeth themselves limits the possibility of performing intricate oral procedures and obtaining sufficient volume and size of samples, including fluids (e.g., blood, crevicular fluid, etc.), and tissues (e.g., jawbones, periodontal tissues, organs, etc.,).

Large vertebrate species, such as the rabbit, dog, sheep, and pig, have advantages over small vertebrates. These include that oral interventions and procedures commonly performed in humans are often feasible due to the larger size of the mouth and teeth. In addition, it is generally possible to obtain sufficient sample volumes and sizes to test multiple endpoints in the same animal. Another advantage of large vertebrate species is that, as in humans,

the cortical bone in craniofacial and postcranial skeletons possess Haversian systems and intracortical bone remodeling.

A critical element to consider is the *relative replacements emphasized in animal research concerning the 3Rs*[61]. This concept states that replacing any vertebrate with a nonvertebrate species or replacing a vertebrate species with a vertebrate or nonvertebrate species is lower on the phylogenetic scale when comparable data can be obtained, should be done. Thus, for this principle of humane animal experimentation, it is preferable to limit the use of rabbits, dogs, pigs or sheep, to circumstances in which they produce unique data.

D.1. Small vertebrates:

The rat (*Rattus norvegicus*) is the most commonly used species in preclinical MRONJ research. We identified 145 articles utilizing rats (Figure 1). Investigators purposely developed MRONJ models by associating different pARs (e.g., N-BPs, anti-RANKL antibodies) with various oral risk factors. Since tooth extraction is the most frequent oral risk factor associated with MRONJ in humans[5, 6], it is not surprising that ~75% of the *in vivo* rat studies (n= 109) involved tooth extraction (Figure 2A, Table 2). Extractions of one or more maxillary or mandibular molars were conducted in anesthetized rats using dental explorers, surgical curettes, and/or small forceps. While performing this procedure, researchers frequently reported that an apical portion of a root could break off and remain within the tooth socket, creating root retention. This is more common in older rats that tended to suffer dental ankylosis. The experimental outcomes (e.g., MRONJ incidence, healing, inflammation, regeneration) could be affected when root retention occurs. Thus, they have recommended that data from rats with incomplete tooth extraction be excluded.

Most studies that involved tooth extractions were conducted on healthy molars after or during treatment with pARs (n=109; Table 2;). The investigators reported either necrotic bone, though never supported by histologic evidence of exposure to the oral cavity[62–66], or absence of bone necrosis[67, 68]. For example, rats treated with clinically relevant doses of ALN (cumulative dose of 1.2 mg/kg during 14 wks) or intraoral injections with ALN (cumulative doses of 4 mg/kg during 2 wks) that underwent extraction of a healthy molar experienced a transient inhibition of healing during the early phases of socket healing. No histologic evidence of necrotic bone at any stage was observed[67, 68]. In contrast, rats that received supra-clinical doses of ALN, with cumulative doses of 12 mg/kg SC during 12 wks (10X higher than that used by[68]) and 3X higher than the cumulative dose used by[67]) developed non-exposed necrotic bone or bony sequestra, and delayed socket healing[66]. In contrast, when rats underwent a healthy molar extraction and received a pAR (ALN, ZOL, or PAM) with co-adjuvant glucocorticoid therapy, they often developed histopathologic evidence of exposed necrotic bone or bony sequestra[62, 64, 69–71].

Six percent of rat studies (n= 8) utilized experimental periodontitis as the oral risk factor (Figure 2A, Table 2). Laboratory rats and mice require sustained intervention to create mild to moderate periodontitis because, unlike humans[72–77], these species are not naturally prone to periodontal disease[63, 74, 78, 79]. In the context of MRONJ, experimental periodontitis was achieved by placement of a ligature around a molar[21, 40, 80–84],

repeated injection of LPS into gingival tissues[85], or injection of bacterial pathogens into gingival tissues[82, 86].

Only two percent of rat studies (n= 3) used periapical infection alone as an oral risk factor for MRONJ[87–89]. Periapical infection was produced by exposing the pulp of one or more molars through the occlusal surface using a round bur and, in some cases, inoculating the exposed pulp with periodontal pathogens[90, 91]. Rats subjected to experimental periodontitis or periapical infection that concurrently received ZOL (66–200 μg/Kg) developed histopathological lesions compatible with osteonecrosis[21, 82, 88]. However, only one study[21] reported histopathological evidence of necrotic exposed bone and reported MRONJ prevalence (~20%). Two other studies that used rats with experimental periodontitis and were treated with ALN (1 – 2.5mg/kg SC for three or four weeks) reported histopathologic osteonecrosis[81, 85]. Still, the necrotic bone was not exposed to the oral cavity.

Interestingly, many clinical studies suggest that periodontal or periapical infection of teeth prompts the need for most tooth extractions and increases the risk for MRONJ[20, 92–98]. Thus, several investigators reported *in vivo* rat models (~3%; n=5) combining these oral risk factors. Inflammatory dental disease (e.g., periodontitis, periapical infection) was first induced, followed by extraction of the infected tooth[40, 90, 91, 99, 100]. In most studies, ZOL was used as the systemic risk factor. Indeed, rats treated with ZOL (200–300 μg/Kg IV 2–3x/wk) that underwent extraction of an infected molar developed more extensive alveolar bone osteonecrosis, impaired healing of the extraction socket, and persistent inflammation, compared to the extraction of uninfected teeth. Three of these studies reported exposed necrotic bone[90, 91, 100]. In addition, Hadaya et al.[91] found exposed necrotic bone in the rats that received 10mg/kg of OPG-FC SC for 9 wks.

Four percent of the studies (n=6) used implant placement as a potential oral risk factor for MRONJ[101–106] (Figure 2A, Table 2), using two phases. In the first phase, anesthetized rats were subjected to tooth extraction, usually of the first maxillary molars. In the second phase, an implant was placed in the fresh tooth extraction site or after a healing period of ~4 wks. Titanium mini-implants, titanium self-drilling screws, and/or zirconia implants were used, with 1.2–2.2 mm in diameter and 3 mm in length. One study[104] reported exposed necrotic bone lesions compatible with MRONJ associated with peri-implant bone loss areas.

A few studies (~3%; n=4) utilized models involving trauma to the jaws or gingival lesions (depicted as *Others* in Figure 2A; Table 2)[107–110]. One study used a mandibular angle fracture induced by unilateral mandibular osteotomy[109]. The bone segments were repositioned, and fixation was created with a stainless steel wire at the inferior border of the mandible. In other studies, a mandibular defect was made by grinding the jaw bone with a slow speed drill, which was left exposed with denuded gingiva[108, 110]. Finally, others used a curette to induce approximately 3 X 1.5 mm gingival wound in the palatal mucosa between the first molar and the great palatine canal to denude the alveolar process[107]. Two of these studies reported MRONJ but neither reported prevalence nor confirmatory histopathologic evidence of exposed necrotic bone[109, 110]. Another of these studies did not find MRONJ lesions but reported inhibitory effects of ZOL on bone healing

without detrimental impact on soft tissue healing[107]. Seven percent of the studies (n= 10) were performed with no oral risk factors to directly study the effects of pARs on healthy craniofacial bones[111–120] (Figure 2A; Table 2).

Furthermore, whereas most MRONJ rat studies utilized an N-BP (ALN, ZOL, PAM) as the systemic risk factor, only two MRONJ studies in rats used RANKL inhibitors[91, 121]. Regarding the subject matter of rat studies, we found that most of the studies were mainly focused on translational research (~38%; n= 55), preventive and curative treatments (37%; n= 54), and characterizing an animal model for the disease (19%; n=28). Only a few involved basic research or mechanistic studies (~3%; n= 5) or the investigation of drugs associated with MRONJ other than pARs (2%; n= 3) (Figure 2B).

Of the 54 studies investigating preventive and curative treatments, 41 involved preventive therapies (Supplemental Table 1). Some of the investigated preventive treatments included PTH[105, 122–127], laser therapy[128–130]; photodynamic therapy[131, 132], hyperbaric oxygen therapy[133, 134], resveratrol[84, 135], local chelation of the alveolar bone matrix using cadmium or EDTA[114, 136], and local transplantation of mesenchymal stem cells (MSCs) or the application of derived products from MSCs[137–139]. Interestingly, other preventive modalities investigated the effects of discontinuation of pARS (OPG-Fc or ZOL) before or after tooth extraction[91, 140]. The curative treatments for MRONJ (n= 13) included several similar approaches to those for preventive treatments (Supplemental Table 1). These included PTH[109, 141–143], injection of platelet-rich plasma into the extraction socket[144, 145], and local transplantation of MSCs, endothelial progenitor cells, or molecular products of MSCs[146–149].

In addition, three percent of the studies (n= 5) focused on investigating mechanisms that could be involved in the pathophysiology of MRONJ. A list of these studies is presented in Supplemental Table 2, highlighting some specific details of the investigations. Finally, Supplemental Table 3 summarizes the rat studies that provided the doses of pARS used and the reported prevalence of MRONJ lesions in the experimental animals.

The mouse (*Mus musculus*) is the second most commonly-used species used for *in vivo* MRONJ studies, with 65 articles (Figure 1). As in the rat, investigators purposely developed MRONJ models by associating different systemic risk factors (pARs [e.g., N-BPs, anti-RANKL antibodies] with various oral risk factors. In 60% of the studies (n= 39), investigators utilized tooth extraction alone as the oral risk factor (Figure 2A; Table 2). Compared to rat studies, a greater percentage of mouse studies used periapical infection (~9%; n=6)[23, 26, 43, 150–153], while comparable to rat studies, only ~5% of mouse studies (n=3) used periodontitis models[154–156] (Figure 2A, Table 2).

Investigators also established murine models and performed *in vivo* studies by combining two oral risk factors, where inflammatory dental disease, either periodontitis or periapical infection, was first induced and then affected molars were extracted. We found five studies (~8%) that used this approach[16, 17, 157–159] (Figure 2A, Table 2). Furthermore, a few mouse studies (~5%; n= 3) used a jaw bone fracture, gingival wound, or a palatal injury as oral risk factors for MRONJ (depicted as *Others* in Figure 2A)[44, 160, 161]. On the other

hand, as in rats, several studies were performed with no oral risk factors (n= 9; ~14%)[162–170].

MRONJ mouse studies have also shown significant outcome variations depending on the systemic and/or oral risk factors utilized in the experiments. Most MRONJ murine studies used N-BPs, particularly ZOL (alone or combined with dexamethasone [DEX] or cyclophosphamide)[16, 17, 19, 26, 150, 152, 154, 171–176] or PAM[157] as systemic risk factors. Fewer studies used RANKL inhibitors[16, 23, 43, 152, 158, 173] or angiogenesis inhibitors[45].

When ZOL was combined with the extraction of a healthy molar, mice tended to developed histopathologic oral lesions characterized by non-exposed necrotic bone[19, 171–173]. Similar findings were observed in mice treated with anti-mouse RANKL antibodies and underwent extraction of a healthy molar[173]. In contrast, when ZOL was administered in combination with dexamethasone, oral histopathologic lesions tended to be more frequently accompanied with exposed necrotic bone or sequestrum formation at the extraction sites[19, 171]. Furthermore, the combination of ZOL, dexamethasone and docetaxel (a potent chemotherapeutic agent) worsened MRONJ like-lesions and increased the prevalence of exposed bone compared to mice treated with ZOL and dexamethasone[171]. Another study showed that when mice were subjected to healthy molar extraction and treated with combination therapy of ZOL and cyclophosphamide (cytotoxic chemotherapy), the oral lesions tended to be more severe and manifest histopathologic necrotic exposed bone and/or bony sequestrum[174].

Notably, when pARs, such as ZOL[26, 150, 152], RANK-Fc, or OPG-FC[23, 43, 152] were administered to mice with natural periodontitis or experimentally induced inflammatory dental diseases (periapical or periradicular disease), exposed necrotic bone was a distinctive histopathologic feature of the oral lesions, except in one study where mice developed non-exposed necrotic bone[150] (Table 2).

The oral risk factors in other murine MRONJ models were developed combining tooth extraction and inflammatory dental disease (Figure 2A; Table 2). Indeed, a few investigators performed *in vivo* murine studies that combined extraction of an infected molar and ZOL or OPG-FC[16, 17] (Table 2). In both studies, extraction of the infected molar triggered extensive osteonecrosis, with impaired healing of the extraction socket and persistent inflammation. In addition, the necrotic alveolar bone was exposed in one study[16].

No murine studies in the MRONJ arena were done utilizing dental implant placement as the oral risk factor. This might be, perhaps, due to the small size of the oral cavity of mice and the technical difficulties in performing this approach compared to rats or larger vertebrates.

Regarding the subject matter of the studies, we found that compared to rats, *in vivo* murine studies were more focused on basic research and mechanistic studies(~37%; n=24), followed by studies for characterizing MRONJ models (~23%; n=15), preventive and curative treatments (20%; n= 13), translational research (~18%; n=12), and investigating drugs associated with MRONJ other than pARs (1.5%; n=1) (Figure 2B).

From the thirteen studies investigating preventive and curative treatments for MRONJ, six involved preventive therapy, whereas seven involved curative experimentation (Figure 2B; Supplemental Table 4). Some preventive therapy approaches included the local application of adipose-derived MSCs, to prevent or reduce the incidence of MRONJ[175, 177] and the local transplantation of BMP-2 adsorbed onto beta-tricalcium phosphate (β-TCP). The BMP-2/β-TCP compound accelerated bone formation and reduced bone necrosis in the tooth extraction socket preventing MRONJ[178]. Other tested preventive treatments included administration of recombinant human PTH before tooth extraction[179], the alternative use of ^{99}Tm-conjugated methylene diphosphonate, instead of ALN, to reduce the risk for MRONJ[180], and the co-injection of etidronate, a non-N-BP that competes with and inhibits the entry of N-BPs (ZOL) into cells associated with inflammation and necrosis and eliminates part of the N-BPs accumulated in bone[164]. The curative treatments for MRONJ tested in murine models were similar to those utilized for preventive therapies. For example, they included the systemic transplantation of MSCs[19, 181], a stromal vascular fraction of adipose tissue[182], and peripheral blood mononuclear cells (PBMCs)[183] to induce immunomodulatory effects and acceleration of tissue repair in mice with MRONJ. Other curative treatments tested in murine models included PTH[184], intraoral injections of a low potency BP that reduced the necrotic bone area of MRONJ lesions[185], and the local injection of the tetrahedral framework of nucleic acids into the mucosa adjacent to MRONJ lesions to promote healing of the oral lesions[186].

A more significant percentage of mouse studies (~37%; n= 24), compared to rat studies (~4%; n= 24), have focused on investigating mechanisms that could be associated with MRONJ pathophysiology. A list of most of these studies is presented in Supplemental Table 5, highlighting some specific details of the investigations. Finally, Supplemental Table 6 summarizes the rat studies that provided the doses of pARS used and the reported prevalence of MRONJ lesions in the experimental animals.

The rice rat (*Oryzomys palustris*) is a rodent species from the Family *Cricetidae*, subfamily *Sigmodontinae,* and Tribe *Oryzomyini*, which is not commercially available. This species was first used for studying periodontitis some years ago[15, 42, 72, 187, 188]. Two models of MRONJ were developed in the rice rat linked to two different types of periodontitis: 1) *a generalized form*, which affects both jaws and is achieved by feeding a high sucrose-casein (HSC) diet[15, 42, 72, 187, 188]; and 2) a localized form, which affects the maxilla, and is achieved by feeding standard (STD) rodent chow[15, 25, 42]. The *generalized* form, similar in appearance and location to moderate/severe generalized periodontitis in humans[15, 42, 72, 187–189], was first presented many years ago[72, 73, 190]. The rice rat *generalized* periodontal disease model is more familiar to the field than the localized periodontitis model. The rice rat *localized* periodontal disease model is characterized by food/fiber impaction at the lingual aspect of the interdental space between the second and third maxillary molars. Neither form requires mechanical or microbiologic interventions to initiate or maintain the disease[72, 73, 190]. Rice rats with either generalized or localized periodontitis as an oral risk factor that simultaneously received oncologic doses of ZOL as a systemic risk factor developed MRONJ after 12–24 wks ZOL treatment[22, 24, 25]. The prevalence of MRONJ in rice rats depends on the dose and duration of exposure to ZOL, reaching 100% at ZOL oncologic doses by 18–24 weeks of ZOL treatment[22,

24, 25]. Notably, several decades before N-BPs were linked to MRONJ, the presence of "*nonvital*" exposed alveolar bone in rice rats treated for 12–18 wks with clodronate, a non-nitrogen-containing predecessor of the N-BPs, was described[191]. Dose-response studies in rice rats that used ZOL as a systemic risk factor contributed essential data that helped establish a causal relationship between N-BPs and MRONJ in the presence of periodontitis as a local risk factor[24, 25]. MRONJ lesions in rice rats resemble MRONJ lesions in humans. MRONJ lesions in rice rats are histopathologically characterized by areas of exposed necrotic alveolar bone, osteolysis, periodontal tissue destruction, an increased number of dead osteocytes, and fields of adjacent empty osteocyte lacunae[22, 24, 25, 41]. Rice rats with localized periodontitis treated with oncologic doses of ZOL that simultaneously receive periodic periodontal cleaning of their localized periodontal lesions showed significantly lower MRONJ prevalence than ZOL-treated rice rats with localized periodontitis that received no periodontal cleaning[41]. This finding parallels periodontal maintenance therapy outcomes in cancer patients receiving oncologic doses of ZOL[192–194]. Feeding ZOL-treated rats a nutritionally similar rodent chow that replaces the insoluble fiber of the STD diet with soluble fiber (SF) diet prevented the development of both localized periodontitis and MRONJ[41]. The SF diet makes the rice rat resistant to developing localized periodontitis, providing a convenient way to remove the main local oral risk factor for MRONJ in the rice rat.

Rabbits (*Oryctolagus cuniculus*): One group[195] investigating the effects of N-BPs in the context of MRONJ found that local treatment with 2–3mg of PAM inhibited bone healing using a calvaria bony defect model[196]. Others investigated the effects of local stem cell transplantation in New Zealand white rabbits treated with ZOL (800 μg/kg) and dexamethasone (10 mg/kg) once a week for 8 wks and subjected to tooth extraction[197]. The study showed that ZOL+DEX treated rabbits that received adipose-derived stem cells had less MRONJ, a more rapid gingival healing, and bone regeneration after tooth extraction than ZOL+DEX control rabbits. Another study investigated the influence of ridge preservation on the healing of extraction sockets under ZOL treatment (50 μg/kg)[198]. The study concluded that ZOL compromised socket healing and induced MRONJ. This study showed that grafting sockets with collagen-coated natural bone mineral did not affect socket healing in ZOL-treated rabbits.

D.2. Large vertebrates:

Dogs (*Canis domesticus*): The dog was among the first species used in preclinical MRONJ studies. Adult female beagle dogs with no oral risk factors were given daily oral ALN for three years (0.2 or 1.0 mg/kg/d)[199]. No animals developed exposed bone in the oral cavity. However, alveolar bone matrix necrosis was seen in the mandible in 0% of VEH dogs, 25% of ALN 0.2 dogs, and 33% of ALN 1.0 dogs ($P<.04$). The investigators concluded that ALN reduces alveolar bone turnover and increases the incidence of bone necrosis in dogs. These researchers also treated dogs for one or three years with oral ALN (0.2 or 1 mg/kg/d) or IV ZOL (0.06 mg/kg 2x/month)[200]. Again, none of the treatments was associated with exposed bone, but all dogs showed low bone turnover. 17–25% of one-year dogs and 25–33% of three-year ALN treated dogs showed areas of bone necrosis in the mandible and ribs, both sites of high natural bone turnover. The authors concluded

that increased prevalence of mandibular bone necrosis was associated with decreased bone turnover rate. However, it was unclear whether the necrotic bone resulted from direct toxic effects of ALN on osteocytes or simply was an indirect effect caused by reduced turnover that slows the removal of all bone, including that which might contain osteocytes undergoing natural death. These investigators also studied the effects of ZOL (0.06 mg/kg IV 2x/month) on healing after extraction of healthy teeth in mature female beagle dogs for three months[201]. One of six ZOL-treated dogs developed exposed bone post-extraction, which eventually led to the formation of a sequestrum consistent with those reported in humans with MRONJ. These investigators also treated mature beagle dogs with ZOL (0.06 mg/kg IV 2x/month), DEX, or ZOL+DEX and extracted a healthy molar 7–8 months after the start of treatment[202]. Though they found no exposed bone, a few animals had severely disrupted healing in extraction sites with an intense periosteal reaction. Another study found that ZOL (0.06 mg/kg IV 2x/month) induced higher levels of apoptosis and lower levels of MMP-9 in oral epithelial cells of one-year-old dogs treated for three months, supporting the notion that N-BP treatment affects the oral mucosa[203]. Another group studied the effects of ZOL (0.1 mg/kg IV per month for four months) on bone remodeling and healing after extraction of a healthy left third premolar and placement of two orthodontic mini-implants per jaw[204]. They found no MRONJ and noted that all extraction sites in ZOL-treated dogs healed uneventfully by four months post-extraction. Others investigated a potential treatment for MRONJ using a local mesenchymal stromal cells (MSCs) transplantation approach to treat a mandibular bone defect in beagle dogs that received ZOL (0.06 mg/kg IM 2x/month) + DEX (5mg/kg IM 4x/month)[205]. Interestingly, the MSC sheet transplantation promoted healing of the wounds four weeks after surgery compared to non-MSC ZOL+DEX dogs. Others[206] assessed the effects of one-year treatment with ALN (3.5 mg/kg/wk orally) or PAM (1 mg/kg/wk IV) on implant placement and found that N-BPs, particularly PAM, hampered peri-implant bone remodeling and negatively affected osteointegration.

Dog MRONJ experiments have been helpful. They were among the earlier experiments showing that extracting healthy teeth in NBP-treated animals does not lead to consistent development of MRONJ. However, the dog model itself has never been used to investigate the crucial role of inflammatory dental disease in MRONJ. Dog experiments raised the possibility that N-BPs may cause MRONJ *indirectly* by slowing the removal of dying/dead bone *of any origin*, allowing it to accumulate in detectable amounts as MRONJ lesions. However, without consistent OVX-induced bone loss in the female beagle, it will remain difficult to determine a clinically relevant dose of BPs in the dog.

Pigs (*Sus scrofa*): Minipigs possess some physiologic features that make them good animal models to study bone biology and skeletal disorders, such as the existence of non-seasonal estrus, estrogen deficiency-related bone loss, and comparable bone turnover parameters to those in humans[207, 208]. Furthermore, the anatomy of the jaws and teeth, oral microbiome, and structural properties of pig bones resemble those in humans[209–211]. A review of animal models for MRONJ[212] concluded that the minipig is a suitable animal model for MRONJ, based solely on the consistent reproducibility of the disease and the anatomical and biologic similarities of the oral bones and teeth to humans. Seven preclinical studies of MRONJ in pigs were found. The first MRONJ model in this species

was published in 2012[213]. Göttingen minipigs received 50 μg/kg IV ZOL once weekly for six weeks and underwent extractions of healthy second and third premolars and first molar from both jaws and continued ZOL for another ten weeks. The investigators found that all ZOL-treated minipigs developed clinical and histopathological features of MRONJ and impaired wound healing, while such findings were never present in control animals.

Another group developed an MRONJ model by administering ZOL (~100μg/kg IV every two weeks) for 32 wks and extracting a healthy first mandibular molar after 24 weeks of ZOL[214]. Next, the investigators tested a therapeutic approach using bone marrow mesenchymal stem cells (BMMSC) transplantation. The study showed that allogeneic BMMSC transplantation enhanced mucosal and bone healing, increased Tregs, and reduced IL-17 levels in peripheral blood of minipigs with MRONJ. In another study, domestic pigs were given ZOL (~40μg/kg IV once weekly) (N=3/group)[215]. After 60 days, healthy maxillary second and mandibular third molars were extracted. No pigs developed clinical or histopathological MRONJ, though ZOL-treated pigs developed radiographic findings compatible with the disease. Another model used 20-wk-old Göttingen minipigs treated with ZOL (50 μg/kg IV weekly) for 20 weeks after extracting four healthy mandibular premolars[216]. Another group investigated preventive measures for MRONJ and the role of pAR discontinuation in the prevalence of MRONJ[217], using the above model under somewhat different experimental conditions[216]. About 80% of ZOL-treated minipigs developed MRONJ after extraction of a healthy tooth. In contrast, only 40% developed MRONJ when they received a drug holiday of 6 weeks before tooth extraction with preventive wound management plus antibiotic therapy for eight weeks. As all these measures aim to avoid local infection and alleviate the effects of remodeling suppression, the authors suggested that pAR treatment and bone infection are critical in the pathogenesis of MRONJ. Two other studies investigated different aspects of MRONJ in this species[213, 218].

Sheep (Ovis aries): Sheep possess a healing capacity comparable to that of humans[219], making them potentially interesting for studying bone remodeling[220] and osteoporosis[221]. An MRONJ model was developed in Swiss mountain sheep by administering ZOL (75 μg/Kg IV q3wks) for 16 wks, followed by the extraction of healthy first and second mandibular molars, followed by an additional 16 weeks of ZOL[222]. Using similar protocols, the same group induced MRONJ in OVX low-calcium diet sheep by administering ZOL weekly for 16 wks[223]. Others developed a different model of MRONJ in OVX ewes[224]. Sham or OVX ewes were treated with ZOL (~100 μg/Kg IV q4wks) for one year, followed by a healthy first mandibular molar extraction. Two years later, ewes received a dental implant at the extraction site and were sacrificed 2.4 years later. One-third of the ZOL-treated sheep (2/6) developed MRONJ at the mandibular extraction site. The implants remained in place in the control SHAM and OVX ewes but were lost in all ZOL-treated SHAM and OVX ewes.

E. Conclusion

Complete parallelism of the individual *in vivo* animal models with human symptoms rarely exists. We view the current state of animal models for MRONJ as good. Relatively economical small animal models in laboratory rats and mice that are convenient and

produce outcomes that match the tissue level behavior of human MRONJ have encouraged large numbers of investigators to do relevant experiments with substantial numbers of animals. Systematic manipulation of local oral risk factors that involve inflammatory dental disease, particularly in rodents, has made the models more relevant. Such models may eventually allow a close match of mechanisms by subsequent molecular and/or enzyme level characterization. Research in rodents, mainly the rat, and to a lesser extent the mouse, has contributed relevant preclinical models that combine systemic administration of pARs with one or more oral risk factors (e.g., tooth extraction and inflammatory dental disease) long known in humans. They produce clinical and tissue-level pathology that models MRONJ in humans in a reasonable timeframe. Models that use clinically relevant doses of ZOL as used in oncology and osteoporosis patients now exist in the presence of oral risk factors. The most pertinent models avoid using additional agents (e.g., glucocorticoids) because MRONJ routinely occurs in humans without these conditions. Experiments have been done by various approaches that demonstrate that eliminating the oral risk factors reduces the risk of MRONJ, just as eliminating oral risk factors from humans reduces the risk of MRONJ[20, 92–98]. The use of pre-clinical MRONJ models involving uninfected teeth extraction, particularly considering that most tooth extractions in humans involved infected teeth, is no longer state-of-the-art. Pre-clinical small laboratory animal models that involve inflammatory dental disease with or without tooth extraction appear to be sufficiently developed to be used for testing preventions and treatments.

Numerous studies showed that mice and rats treated systemically with a pAR with concurrent oral risk factors developed osteonecrosis. However, the osteonecrotic bone was frequently not exposed to the oral cavity. Thus, these studies may be reproducing stage 0 lesions, representing a potential opportunity to model this stage of the disease. However, further studies are required to demonstrate that exposed necrotic bone eventually occurs to confirm the existence of MRONJ.

We also observed a significant variation in the criteria used to define MRONJ, particularly among small vertebrate studies. For example, in some studies, investigators considered only gross endpoints, while in other studies, investigators utilized histologic approaches, either qualitative or quantitative endpoints, or immunohistochemical/molecular approaches.

It would be highly desirable to establishing and standardizing the criteria for defining MRONJ across the different models. In this case, similar features as human MRONJ lesions should be considered, including the presence of exposed necrotic bone and the histopathologic confirmation of oral bone areas with empty osteocyte lacunae, particularly for small vertebrates.

Models in larger species, particularly the pig, produce accurate clinical and histopathologic outcomes. Still, they have the dual disadvantages that few investigators have the facilities to use such models and the group sizes that can realistically be employed are often relatively small. In addition, the development of MRONJ does not appear to require the presence of Haversian remodeling, a skeletal feature that is often cited as an advantage of large animal models for bone. The role of large animal models may thus be to confirm specific crucial findings from rodent research conducted in multiple laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

This research was supported by the National Institute of Dental and Craniofacial Research (NIDCR), R01DE023783–01A.

Abbreviations listed by order of appearance in the text

AAOMS	American Association of Oral and Maxillofacial Surgeons
AgIs	angiogenesis inhibitors
ALN	alendronate
BRONJ	Bisphosphonate-related ONJ
BP	bisphosphonate
DEX	Dexamethasone
IV	Intravenously
MRONJ	medication-related osteonecrosis of the jaw
N-BP	nitrogen-containing BP
ONJ	Osteonecrosis of the jaw
PAM	pamidronate
pAR	powerful antiresorptive
RANK	receptor activator of nuclear factor kappa-B
RANKL	RANK ligand
ZOL	zoledronate

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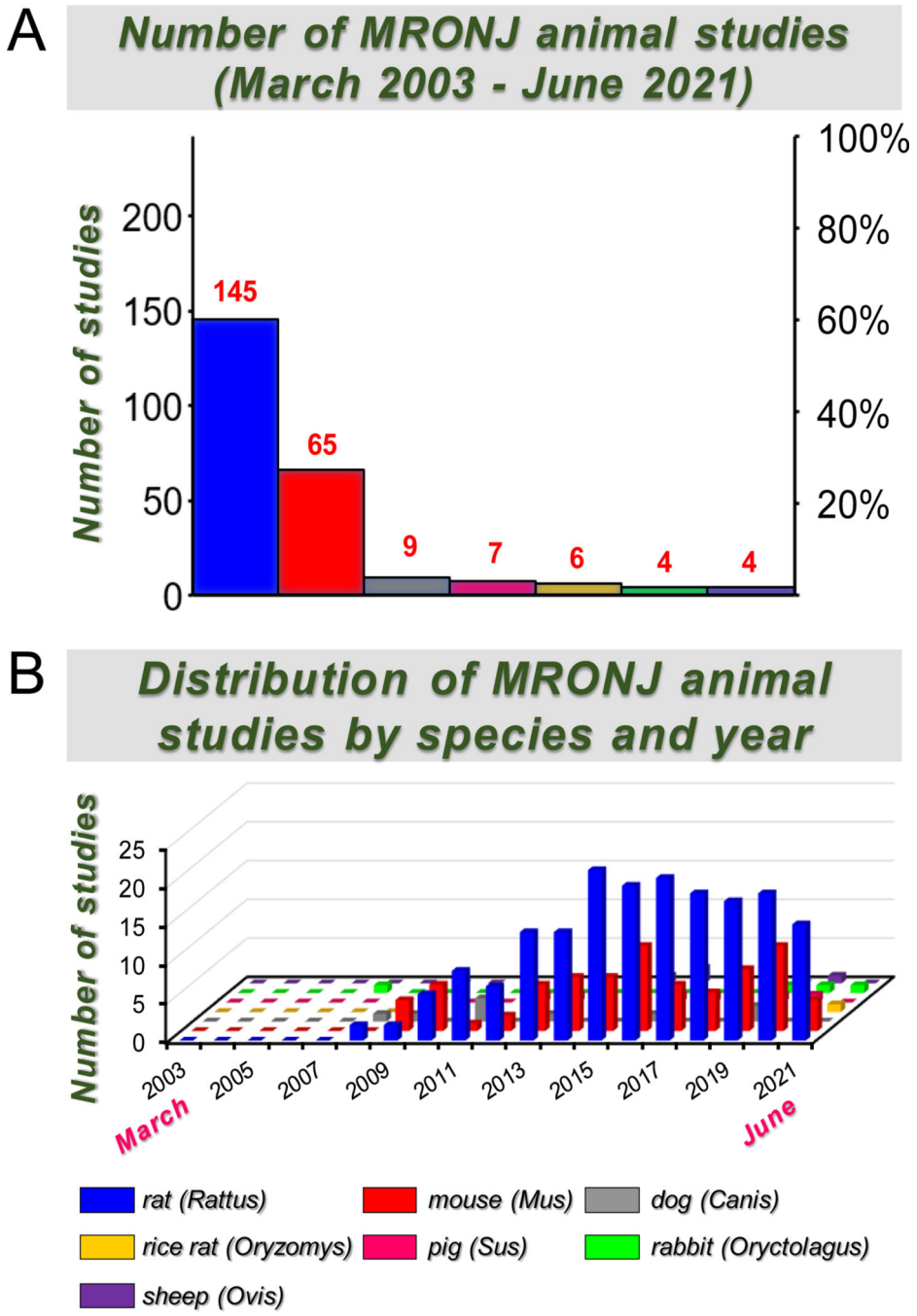

Figure 1. MRONJ animal studies between March 2003 – June 2021.

A. The number and percentage distribution of MRONJ animal studies by species are displayed. **B.** Distribution of MRONJ animal studies by year and species.

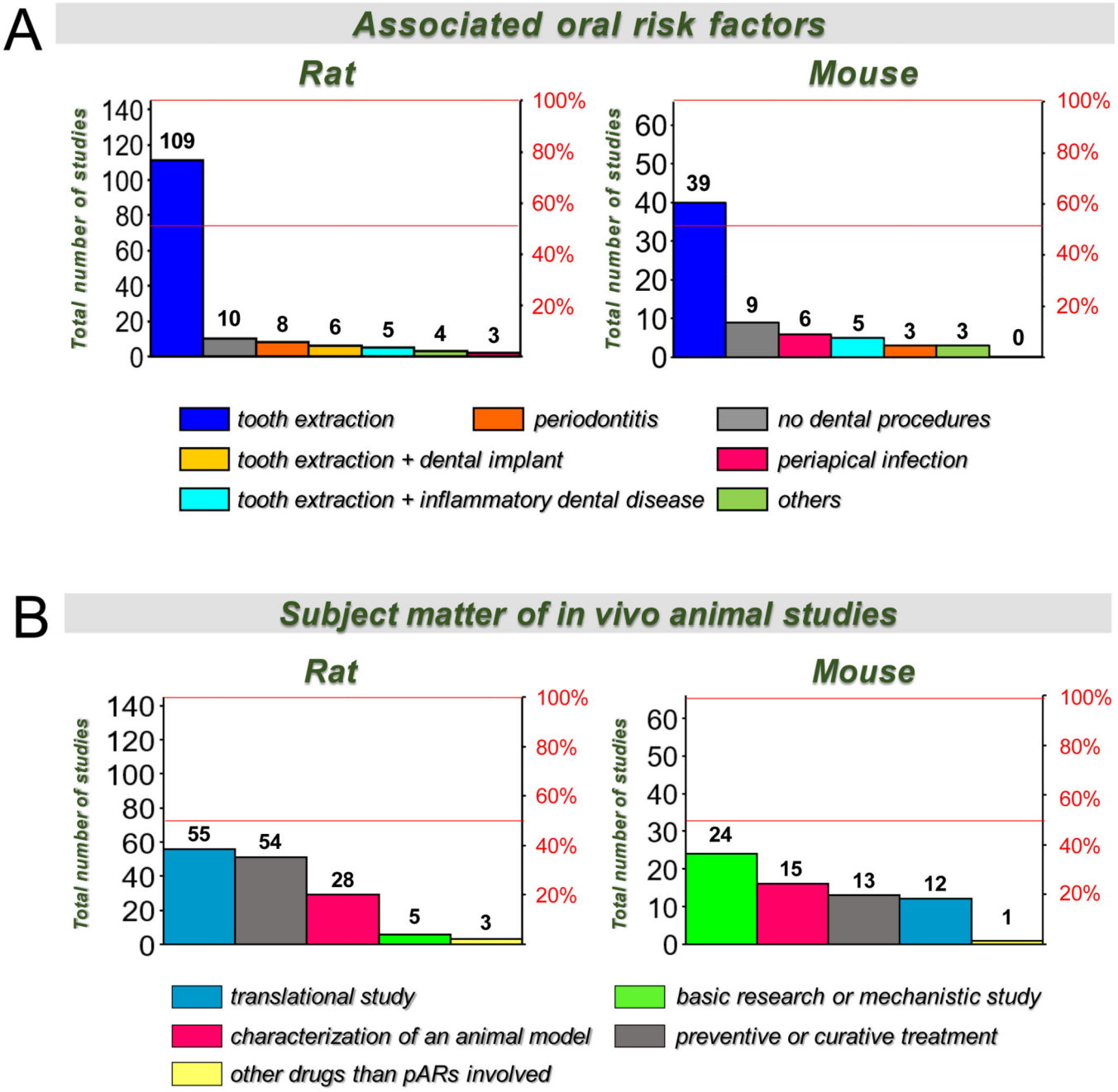

Figure 2. Distribution of MRONJ studies conducted in rats and mice according to the utilized associated oral risk factor and the subject matter of the investigation.

A. Number and percentage distribution according to the utilized associated oral risk factor.

B. Number and percentage distribution of the rat and mouse studies according to the subject matter of the investigation.

Table 1A:

Clinical and pharmacologic features of different N-BPs

Drug	*Disease*	*Dose*	*Route*	*Potency (vs. ALN)*	*Cumulative Annual Absorbed Dose (mg)*
Alendronate	Osteoporosis	70mg/wk	Oral	1*	26
Risedronate	Osteoporosis	35mg/wk	Oral	1.5	13
Ibandronate	Osteoporosis	150mg/mo	Oral	4	8
Ibandronate	Osteoporosis	2mg/3mo	IV	4	8
Zoledronate	Osteoporosis	5mg/yr	IV	15	5
Minodronate	Osteoporosis	25mg/wk	Oral	2.5	9
Ibandronate	Cancer	8mg/mo	IV	4	96
Zoledronate	Cancer	4mg/mo	IV	15	48

*Alendronate potency arbitrarily expressed as “1”. All other BPs are more potent than alendronate[225].

Table 1B:

Clinically relevant doses for zoledronate in the rat and mouse

Species/Disease	*Osteoporosis*	*Cancer*
Rat	8μg/kg/mo IV[a]	80μg/kg/mo IV[*]
Mouse	~20–40μg/kg/mo IV[*]	~200–400μg/kg/mo IV[*]

[a]-actual;

[*]-predicted; IV: intravenous administration

Table 2:

References of rat and mice studies distributed by the utilized associated oral risk factor

Associated oral risk factor	*Rat studies*	*Mouse studies*
Tooth extractions of healthy molars	[62], [67], [226], [63],[64], [68], [227], [228], [229], [230], [65], [231], [70], [232], [71], [233], [141], [234], [235], [236], [144], [237], [238], [146], [239], [240], [241], [242], [243], [128], [244], [123], [69], [245], [246], [140], [247], [248], [249], [250], [251], [252], [133], [253], [147], [66], [254], [255], [256], [124], [257], [258], [259], [260], [129], [261], [262], [121], [263], [264], [265], [266], [267], [142], [136], [268], [130], [149], [131], [132], [269], [270], [271], [272], [273], [134], [145], [126], [274], [275], [148], [276], [277], [135], [143], [278], [279], [280], [281], [139], [282], [283], [284], [285], [286], [287], [125], [288], [289], [127], [290], [138], [122], [291], [292], [293], [294], [130], [137], [295]	[172], [19], [171], [180], [296], [297], [173], [298], [299], [300], [301], [302], [181], [303], [304], [182], [45], [174], [158], [305], [185], [306], [175], [183], [307], [308], [184], [176], [309], [310], [311], [312], [186], [178], [313], [153], [179], [314], [184], [315]
Periodontal disease	[80], [21], [86], [81], [82], [83], [85], [84]	[156], [155], [154]
Periapical infection	[87], [88], [89]	[43], [23], [152], [151], [16], [17], [150], [26]
Inflammatory dental disease + tooth extraction	[90], [40], [99], [91], [100]	[157], [16], [17], [158], [159]
Tooth extraction + dental implants	[103], [102], [101], [105], [104], [106]	None
Other procedures	[107], [108], [109], [110]	[161], [44], [160]
No Dental interventions	[120], [119], [118], [117], [116], [115], [114], [113], [112], [111], [113]	[162], [163], [164], [165], [166], [167], [168], [170], [169]